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EXAMINER

HM12/0227

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ART UNIT | PAPER NUMBER

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DATE MAILED: 02/27/01

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 11-2-00 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~0~~ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-53 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-53 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

DETAILED ACTION

the request for the extension of time and amendment filed on 11-2-00 are acknowledged.

Claims included in the prosecution are 1-53.

Claim Objections

1. **The amended claims do not comply with rule 121 (b). These claims should be resubmitted.**

Claim Rejections - 35 U.S.C. § 112

2. **The following is a quotation of the first paragraph of 35 U.S.C. 112:**

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

3. **Claims 1-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for drop in blood pressure as the adverse reactions and indomethacin as the drug which can treat this pressure drop, does not reasonably provide enablement for generic 'adverse reactions' and 'anti-inflammatory agent'. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. .**

Instant invention is based on the observation that liposomes made with specific phospholipids cause a drop in blood pressure and that indomethacin is able to correct this blood pressure drop. Indomethacin might come under the classification of 'anti-inflammatory drugs' because it has anti-inflammatory properties; just because indomethacin also possesses blood pressure modulating properties, one cannot conclude that all anti-inflammatory agents which is a generic name and includes a variety of compounds are also blood pressure modulating agents. Applicants have provided no rationale for this concept. Secondly and most importantly, liposomes are known in the art as drug delivery agents for the past 20 years and as the prior art would indicate that even the administration of empty liposomes is known. Applicants have not shown that or provided adequate description as to what other adverse reactions are caused by the liposomes and presented a rationale for the capability of indomethacin to correct all the adverse reactions. Broad claims must have broad basis of support in the specification; in the absence of such support, claims must be limited to liposomes made with specific phospholipids and the drop in blood pressure as the adverse reaction and indomethacin as the compound which is able to correct this adverse reaction.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant first of all argues that this rejection does not apply to claims 1-17 because they recite a drop in blood pressure. Applicant is incorrect since these claims recite generic anti-inflammatory agents. Applicant argues that the term, 'anti-inflammatory

agent' is well known in the art. The examiner agrees, but that is not the issue. The examiner is well aware that there are a variety of compounds which come under the generic term 'anti-inflammatory agents' because of their known effect against inflammation. However, instant claims recite 'adverse reactions' and 'drop in blood pressure' and just because one chemical which incidentally comes under the category of 'anti-inflammatory agent', one cannot reasonably come to the conclusion that all chemicals which are classified based on their common function would counter the adverse reactions and drop in blood pressure caused by liposomes. If that were to be the rationale, one could come to the conclusion that just because aspirin prevents heart attacks, Advil, Tylenol and morphine or other similar compounds would also have an effect just as aspirin because they come under the category of 'pain killers'; or just because the heart drug, minoxidil is able to grow hair, other heart drugs would also grow hair. The examiner has provided sufficient scientific basis for his position and applicant has not provided convincing arguments to overcome this rejection. The rejection is maintained.

Claim Rejections - 35 U.S.C. § 102

4. **The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:**

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. **Claims 45 and 47, are rejected under 35 U.S.C. 102(b) as being anticipated by JP 60152414 or JP 63264517.**

Both JP references disclose liposomes containing indomethacin (note the abstracts) and a method of treatment. Instant claim language does not does not exclude liposomal indomethacin taught by the references.

6. **Claims 18, 19, 21, 23, 24, 25, 27, 33-36, 43-45 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Young (5,023,087).**

Young discloses a method of treating an animal with liposomes containing an anti-inflammatory agent (steroids) and empty liposomes; the liposomes are either unilamellar or multilamellar (note the abstract, col. 4, line 62 et seq., col. 10, line 35 et seq., examples). Young meets the limitations of instant composition claims since the steroid is not encapsulated in the same liposomes. That is, Young discloses empty liposomes and the steroid is not in the same liposomes. Since instant claims do not recite any specific bioactive agent, water present in the liposome cavity reads on instant claims since water is bioactive, meaning that it participates in biochemical reactions.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Young is concerned with delivering a drug entrapped in lipsomes rather than counter-acting the adverse reactions caused by liposomes. This argument is not found to be persuasive since Young uses the same liposome composition and an anti-inflammatory agent; in essence, Young discloses the same method of administration; therefore, any adverse reactions caused by liposomes and their reduction by the anti-inflammatory agent which is also administered is inherent in Young, whether they are recognized by Young or not. Applicant's arguments with regard to the composition claims have been noted, but are not found to be persuasive. Instant claims do not recite 'unencapsulated anti-inflammatory agent'. The claims require only that the anti-inflammatory agent be not in THE liposomes (see claim 25 for instance). Young teaches two populations of liposomes and the steroids are in one set of liposomes and the other liposomes are empty.

Claim Rejections - 35 U.S.C. § 103

7. **The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:**

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

8. **Claims 18-32, 34-35, 41-42, 45, 47, and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young cited above by itself or in combination with JP references cited above.**

Young does not teach non-steroidal anti-inflammatory agents. However, it is deemed obvious to one of ordinary skill in the art to use any anti-inflammatory agent including indomethacin if the adverse reaction from the liposomal administration is inflammation; one would be motivated further to administer indomethacin since JP references teach the use of indomethacin for such a purpose.

9. **Claims 33-44 and 48-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young cited above, further in view of Park (BBA, 1992): or Park in view of Young.**

What is lacking in Young is the teaching the modification of the surface of the liposomes using carboxylic acids.

Park teaches that liposomes modified with carboxylic acids prolong the circulation of the liposomes (note the abstract). Park's teachings are generic with respect to the active agent incorporated.

The modification of the surface of the liposomes of Young using carboxylic acids would have been obvious to one of ordinary skill in the art since such a modification results in the liposomes having longer circulation. Alternately, to encapsulate an anti-inflammatory agent as the active agent in the liposomes of Park would have been obvious

to one of ordinary skill in the art since liposomes are known drug delivery agents and the reference of Young shows the knowledge in the art of encapsulation of anti-inflammatory agents in liposomes for delivery.

Applicant's arguments have been fully considered, but are not found to be persuasive.

Applicant while conceding that it may be correct to modify the teachings of Young in view of Park to include carboxylic acids in the liposome structure, claim 33 teaches a composition comprising a liposome in combination with an anti-inflammatory agent. This argument has been addressed above.

10. **Claims 29-32 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 63264517 or Young cited above by themselves, in further in view of Park (BBA, 1992): or Park in view of either of Young or JP as set forth above, and in further combination with Cheng (Investigative Radiology, vol. 22, 1987) .**

The references of JP, Young and Park do not teach the inclusion of a contrast agent in the liposomes. Such an inclusion however, would have been obvious to one of ordinary skill in the art if the purpose is to locate the treatment site as well as treat it since the reference of Cheng shows the awareness in the art of encapsulating contrast agents in liposomes (note the abstract).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Cheng does not teach the use of the contrast agent in conjunction with the anti-inflammatory agent. This argument is not found to be persuasive since the reference of Cheng shows the use of liposomes for imaging purposes and it is within the skill of the art of medicine to image the tissue which needs to be treated and treat it at the same time.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.

Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

February 26, 2001